President's stem cell research picks - March 2011

President's Update on Advances in Stem Cell Science

Highlights of recently published papers from CIRM grantees and other leading research teams around the world.

Yet another type of stem cell -- induced conditional self-renewing progenitor cells

CIRM-funded researchers at the Sanford-Burnham Institute led by Evan Snyder, along with researchers from Korea, British Columbia and Harvard Medical School published their results in the March 4 issue of the *Proceedings of the National Academy of Sciences*.

The usual path to reprogramming involves taking skin cells and redirecting them into pluripotent cells and then differentiating those cells into the desired tissue. By contrast, the Sanford-Burnham team started with neural progenitor cells and added a single gene that successfully instructed the cells to self?renew in a laboratory dish, something they generally will not do. Once they had sufficient cells for transplant the team placed them in a rodent model of stroke where the cells stopped proliferating and differentiated into appropriate neural cells and resulted in improved brain function.

The “conditional” in the name of these new cells comes from the way the gene for selfrenewal is inserted and expressed. The researchers used a viral vector to insert the gene v-Myc into the progenitor cells. The v-Myc version is generally considered safer than other forms of this potentially cancer-causing gene. Also, it is only expressed in these cells under the condition when tetracycline is in the cell culture. When tetracycline is removed, the cells cease dividing and start differentiating. The team suggested that this Induced Conditional Self-renewing Progenitor (ICSP) approach could be used with other organ systems.

More differences found between embryonic and induced pluripotent stem cells

CIRM grantees from UC San Diego and the Salk Institute along with colleagues from Wisconsin, Harvard, Toronto, Helsinki and Bonn published three papers in the March 3 *Nature* that further define some of the genetic differences between iPS cells and embryonic stem cells and between iPS cells and the adult cells of their origin. Some of these differences had been suggested in earlier studies.

In the same issue of the journal, CIRM grantee Martin Pera from the University of Southern California wrote a “News and Views” column analyzing the three papers. Pera concluded that the reprogramming and subsequent expansion of iPSCs in culture can lead to the accumulation of diverse abnormalities at the chromosomal, subchromosomal and single nucleotide base levels. By several measures, iPSCs display more genetic and epigenetic abnormalities than do either embryonic stem cells or their originating fibroblasts.Abnormalities arise at different stages with some of the abnormalities being eliminated through long-term adaptation in cell culture. However, the fact that many of the mutations occur in areas involved in cell cycle regulation and cancer is cause for concern.

Taken together, these papers raise cautionary flags for researchers seeking to develop cell therapies from iPS cells. However, they also empower researchers by revealing the types of abnormalities that exist in these cells. Armed with this knowledge, researchers should be better able to assess and assure the safety of iPS cell-derived therapies prior to clinical translation.

New test makes it much easier and faster to tell if cells are pluripotent

CIRM grantee Jeanne Loring and her team at the Scripps Research Institute published results using the new method in the March 6 *Nature Biotechnology*.

The current gold standard test to determine if your cell line is pluripotent is the teratoma assay in which cells are injected into an animal and the formation of teratomas is detected in six to eight weeks. The new method, called PluriTest, uses microarray technology, which enables the simultaneous analysis of thousands of different DNA sequences. The Scripps team created a database of genes that are active in human embryonic and induced pluripotent stem cell lines. Sufficient genes are represented in the database to make the test highly sensitive and highly specific for detecting pluripotent cells. The data analysis takes about 10 minutes so should greatly improve the efficiency of numerous experiments.

Many labs succeeding in differentiating stem cells into desired cell types

- A team lead by S.M. Watt at Oxford in the U.K. published in the February 22 issue of *Blood* the first proof that iPS cells could be matured into immune system B cells. When the research team differentiated its iPS cells under conditions that have successfully promoted lympho?hematopoiesis in embryonic cells, they found similar formation of pre B cells in their iPS cells. They found genomic rearrangements that support pre?B cell identity. This work could point to therapies for certain immune disorders.
- A group lead by H.W. Snoeck at New York's Mount Sinai published in the February 27 *Nature Biotechnology* that they could turn iPS cells into anterior foregut endoderm (AFE). Being able to turn iPS cells into the layer of endoderm known as AFE could expand their use for cell therapy and basic research to tissues important for immune function, such as the
- thymus; for metabolism, such as the thyroid and parathyroid; and for respiratory function, such as the trachea and lung. They pushed the iPS cells to mature into AFE by inhibiting two growth factors, transforming growth factor Beta and bone morphogenic protein.
- A Northwestern University group lead by John Kessler published the first data in which embryonic stem cells were matured into the type of brain cell lost in Alzheimer's in the March 4 issue of *Stem Cells*. Alzheimer's progresses through the destruction of Basal Forebrain Cholinergic (BFC) neurons. By overexpression of two relevant human transcription factors in neural progenitor cells derived from embryonic stem cells the team was able to generate up to 94 percent pure BFC neurons. The resulting BFC cells could be sustained in culture indefinitely making them an immediate tool for testing potential drug therapies. More long term is the potential of cell replacement therapy; the team did implant the cells in mice and were able to detect the growth of connecting fibers and what appeared to be normal function.
- Industry scientists, at Advanced Cell Technologies, and academic researchers, at Harvard, Seoul and Illinois, published in the January 11 *Cell Research*, data showing human embryonic stem cells could be used to generate blood platelets.
- Starting with human embryonic stem cells the team generated blood platelets on a large scale that were indistinguishable from normal platelets. They were similar in size and behaved the same helping to form clots in the lab dish and in mice who had sustained injuries.

Short-term immunosuppression promoted engraftment of pluripotent stem cells

CIRM-supported Joseph Wu and his team at Stanford published data in the March 4 *Cell Stem Cell* showing that short-term immunosuppression was sufficient to enable engraftment of embryonic and induces pluripotent stem cells as well as more differentiated derivatives.

The team was able to block leukocyte co-stimulatory molecules to avoid immune system rejection of the transplanted cells and enable their engraftment, which was sustained for at least 28 days. Mice were treated four times over six days with three co-stimulatory blocking agents: cytotoxic T?lynphocyte-associated antigen, anti?CD40 ligand, and antilymphocyte function-associated antigen.

The study still needs to be verified in human transplants, but if this level of tolerance is verified it could go a long way toward ensuring that stem cell?derived tissues can survive long enough to engraft and generate a therapeutic benefit.

Cells from patient with rare disease yield model for aging in a dish

CIRM grantee Juan-Carlos Izpisua Belmonte and his research group at The Salk Institute reported in the February 23 issue of *Nature* that they were able to create an iPS cell line from a patient with a rare premature aging disorder and mature them into smooth muscle cells that displayed the signs of vascular aging.

The valuable disease-in-a-dish model was derived from a patient with Hutchinson-Gilford progeria, which causes the individual to age eight to 10 times faster than normal. The disease is caused by a single point mutation in the gene encoding lamin A, which in turn leads to production of a shortened version of the protein progerin and that leads to a host of problems associated with aging. In the iPS cells created at Salk the biological clock was reset and lamin A was silenced, so the reprogrammed cells did not retain the memory of what they had been. But, when the team differentiated them into smooth muscle the mutated lamin A and progerin expression was reactivated and the muscle cells had the phenotype of premature aging, including misshapen nuclei.

This cell line could become a robust model for unmasking the progression and complexity of the aging process making it easier to study the pathogenesis of cardiovascular and other aging-related disorders.
